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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,820	07/21/2000	Alan D. Attie	960296.97290	4397

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EXAMINER

QIAN, CELINE X

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 07/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/620,820

Applicant(s)

ATTIE ET AL.

Examiner

Celine Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 13-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: sequence letter.

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DETAILED ACTION

Claims 1-16 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the method of Group I is related to the fusion protein of Group II since the method is directed to the expression of the fusion protein, and search for both groups is not a serious burden. This is not found persuasive because the method of Group I and the fusion protein of Group I are patentably distinct. The method of Group I is directed to the using of a DNA construct encoding the protein of Group II. However, the fusion protein of Group I is not limited to the use for a method of lowering cholesterol as claimed in Group I. The fusion protein of Group II can also be used to make an antibody. A search of Group I is not co-extensive with a search of Group II; therefore, there is a burden to search both groups.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 13-16 are withdrawn from consideration for being drawn to non-elected subject matter. Claims 1-12 are currently under examination.

Information Disclosure Statement

It appears that there is one reference, attaching to Twisk et al. (2000), is not listed on the 1449 form. If applicants intend to have the examiner to consider the reference, it needs to be listed on the 1449 form. Otherwise, the examiner will disregard the reference.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

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this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Specification

The specification is objected to because of the following informalities: 1) "The Brief Description of the Several Views of the Drawing" does not specify which example the data represents. 2) The label for X and Y axis of the graph in Figure 1 is missing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7, 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses that a soluble truncated low density lipoprotein receptor (LDLR), LDLR354, tagged with ER retaining signal KDEL, is able to decrease apoB secretion in vitro and in vivo thus reduce LDL synthesis. However, it is well known in the art that LDLR family is composed of a class of cell surface endocytic receptors. Clearly, the membrane bound

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form of LDLR would not have such effect since it cannot be retained in ER. In addition, the specification does not teach which part(s) of the LDLR354 is functional in such effects, and whether such fusion protein made with other soluble LDLR (i.e. Rubinstein et al., 1993. EP0553667) would have similar effects. Therefore, recitation of "a low density lipoprotein receptor" in the claims is not an adequate description of the invention. Applicants may overcome this rejection by using terminology which refers to only the LDLR that is capable of decrease apoB secretion. Whatever terminology used by applicants must also enjoy support by the present specification.

Claims 1, 3-5, 7, 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the lowering of serum cholesterol or glyceride levels in an individual comprising the steps of: preparing a nucleic acid construct comprising a DNA sequence encoding a fusion protein comprise a soluble LDLR and localization domain operatively linked to a promoter; administering the nucleic acid construct systemically to a mammal, wherein expression and production of said fusion protein results in the lowering of serum cholesterol in said mammal, does not reasonably provide enablement for a method for lowering the serum cholesterol or triglyceride levels in an individual comprising the steps of: making a genetic construct comprising a protein coding sequence encoding for the expression of a fusion protein including any lipoprotein receptor and a localization domain operatively linked to the fusion protein, and delivering the genetic construct into the individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

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The nature of the invention is a method of lowering serum cholesterol or triglyceride in an individual comprising the step of making a genetic construct comprising (1) a protein coding sequence encoding for the expression of a fusion protein including a low density lipoprotein receptor and a localization domain which directs localization of the fusion protein to the interior of a cell in the individual, and (2) a promoter effective in the cells of the individual to express the protein encoding sequence; and delivering the genetic construct into the individual. In the example given in the specification, applicants disclose a fusion protein encoding a truncated soluble LDLR, LDLR354, linked to an endoplasmic reticulum (ER) localization sequence, KDEL, which is capable of decrease hepatic apoB secretion both in vitro and in vivo.

Two references are cited herein to illustrate the state of art of lowering serum cholesterol by using a fusion protein comprising LDLR and a signal peptide which direct the receptor to the interior of a cell. Twisk et al. (2000, The Journal of Clinical Investigation, Vol. 105, No. 4, pages 521-532) state that increased LDLR level reduces apoB secretion in hepatic cells (see page 526, 2nd column, last paragraph). They propose that the interaction between LDLR and apoB in the lumen of ER could make apoB more protease accessible (see page 529, 2nd column, 2nd paragraph). Gillian-Daniel et al. (2000, Abstract from scientific session, supplement to Circulation, Vol. 102, No. 18, Number 720) provide further evidence that by retaining LDLR to ER, it facilitates the degradation of apoB. It is well known that apoB is a necessary component of VLDL/LDL synthesis. Therefore, decreasing apoB secretion would lower serum cholesterol and triglyceride by decreasing VLDL/LDL synthesis. However, full length LDLR does not stay in ER, instead it translocates from cytoplasmic domain to cell surface after post-translational

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modification. To retain the LDLR in ER, not only it needs an ER retaining signal, it also has to be in soluble form.

Applicants have not provided guidance in the specification toward how to make a membrane bound LDLR with ER retaining signal that will stay in ER and interact with ApoB. The specification only teaches that a truncated soluble LDLR354 with KDEL translocating sequence is effective in lowering serum cholesterol. However, the specification does not provide enough information on which domain the LDLR is necessary to such function.

The breath of the claims is broad that including any LDLR family members and in any form. For reasons discussed above, not all those receptors can be used to generate a fusion that will be retained in ER, thus lowering apoB secretion. To attempt to practice the claimed invention, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, the specification lacks sufficient guidance in how to make fusion proteins comprising any LDLR and a localization sequence to lower serum cholesterol. Therefore, it would require undue experimentation for one in the skill of art to make/use the invention commensurate in scope with these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: expression and production of said fusion protein results in the lowering of serum cholesterol or triglyceride in said mammal. This step is necessary because in

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order to practice the invention, one of ordinary skill of art would need to know how delivering the construct into the individual relates to lowering serum cholesterol or triglyceride levels.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 9, 11, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Twisk et al., in view of Teasdale and Jackson. (1996, Annu. Rev. Cell Dev. Biol., Vol. 12, pages 27-54).

The instant claims are drawn to a DNA construct comprising a protein coding sequence encoding a LDLR and KDEL, a ER retaining signal peptide.

Twisk et al. teach that expression of LDLR decreased apoB secretion in a LDLR-/- knockout mouse model (see page 527, 1st column, last paragraph). Twisk et al. further propose a model of apoB secretion and degradation pathway (see page 530, figure 7, and 1st column, 1st paragraph): "As apoB enters the secretory pathway, presecretory degradation occurs via both LDL receptor-dependent and -independent mechanisms. A temporary arrest of apoB translocation, or an extended association between apoB and the translocon as it enters the ER, could facilitate an interaction between apoB and the LDLR. Rapid and slow presecretory apoB degradation may occur in the ER or in a post-ER compartment. The nascent lipoprotein particle ultimately reaches the cell surface, where the LDLR can mediate its reuptake, resulting in internalization and subsequent turnover of apoB." However, Twisk et al. does not teach a LDLR comprising a KDEL ER retaining signal.

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Teasdale and Jackson teach that KDEL is a ER retaining signal that is capable of retrieving soluble KDEL-tagged molecules back to ER (see page 36, last paragraph).

It is well known in the art that apoB is a necessary component of lipoprotein particle, including LDL. It would be obvious to one of ordinary skill of art who intend to lower serum cholesterol in a patient to decrease apoB secretion, thus lower LDL synthesis. Based on the teaching of Twisk et al. and Teasdale and Jackson, one of ordinary skill of art would make a LDLR which would be retained in ER to maximize presecretory apoB degradation. The ordinary artisan would have a reasonable expectation of success because of the teaching of Twisk et al., who teach that LDLR facilitates presecretory apoB secretion in ER and post-ER compartment, and Teasdale and Jackson, who teach that peptide can be retrieved from other compartment to ER by tagging with KDEL. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 2, 6 and 10 are free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0823. The examiner can normally be reached on 8:30-5:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 28, 2002



JAMES KETTER
PRIMARY EXAMINER